REMARKS

Status of the claims

Claims 1, 3, 4, 6-9, 12-21 and 23-34 were pending and under active consideration in the instant application. The independent claims 1, 16, 21, and 23 have been amended. "Providing" has been replaced with "obtaining," which revision Applicants respectfully submit does not constitute new matter. No claims have been added or canceled with this Response. Hence, upon entry of this paper, claims 1, 3, 4, 6-9, 12-21 and 23-34 will remain pending and under active consideration.

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Withdrawn rejections

Applicants wish to thank the Examiner for withdrawing the rejections under 35 U.S.C. § 112, first paragraph, and the provisional rejections.

Claim rejections under 35 U.S.C. § 103

Claims 1, 3, 4, 6-9, 12-21 and 23-34 stand rejected as allegedly being unpatentable over PCT Application No. WO 95/13697 to Reid *et al.* ("Reid") in view of U.S. Patent No. 6,129,911 to Faris ("Faris") and U.S. Patent No. 5,843,024 to Brasile ("Brasile") for the reasons of record. Applicants traverse this rejection on the following grounds.

None of the cited references, alone or in combination, teaches or suggests a method of isolating liver progenitor cells from a liver tissue obtained between about 2 hours and 30 hours postmortem.

In order to establish a *prima facie* case of obviousness, the Office must preliminarily establish that each and every claimed limitation may be found in the prior art. Applicants respectfully submit that the Examiner has failed to meet this threshold requirement. No reference in the art teaches or suggests a method of processing a non-fetal donor liver tissue or procuring

liver progenitor cells from a liver tissue obtained between *about 2 hours and 30 hours postmortem.* At least with respect to the primary reference, the Examiner concedes this fact. Office Action, page 4, para. 1.

Indeed, the Examiner does not appear to contest the fact that *no* reference teaches or suggests a method of processing a non-fetal donor liver tissue or procuring liver progenitor cells from a liver tissue obtained between about 2 hours and 30 hours postmortem. Rather, the Examiner has opted to "cherry pick" choice, sweeping statements in the cited references and "derive[] from the totality of the combined teachings" a notion that the claimed invention would have been obvious to one or ordinary skill in the art at the time the present invention was filed.

For example, while Reid only teaches the isolation of liver cells from embryonic and neonatal livers *immediately* post-mortem, the Examiner notices that Reid professes that "the method of the invention offers a systematic approach to isolating hepatoblasts from any age from any species." Presumably, the Examiner interprets "any age" to include 2 hours and 30 hours after death. Similarly, despite the fact that Faris only teaches the isolation of cells *immediately* following anesthetization of the donor, the Examiner notices that Faris professes that the isolation method may be performed on "mammalian organ donors including deceased donors or cadavers." Finally, with respect to Brasile, notwithstanding its silence on stem cells altogether, because Brasile teaches the "resuscitation" of whole livers post-mortem, the Examiner presumably takes this teaching to imply that stem cells could also be isolated from the livers so "resuscitated."[1]

The fact remains, however, whether the references are taken alone or in combination, "[t]his invention was completely unexpected, since all known prior art references regarded ischemically damaged organs as being totally useless for any meaningful purpose" and that the

[1] Applicants do not doubt the validilty of the claims issued with Brasile as suggested by the Examiner. Page 9, 1st para. of the Office Action. Rather, Applicants highlight that even if Brasile's resuscitation solution were to "reverse" impairment of liver *function*, there is no teaching or suggestion that functional liver progenitors *per se* can be isolated from these "impairment-reversed" livers."

present inventors were the first to take advantage of the discovery that progenitors were actually *resistant* to ischemia. [Specification, para. 0016] This notion is further supported by the Declaration of Dr. Neil Thiese, being submitted herewith. Dr. Theise, who is an expert in hepatic stem cells, attests that at the time of invention, the idea that hepatic stem cells could be isolated from livers greater than about 2 hours postmortem was met with "doubt, if not derision," by the majority. Declaration at 9-10.

There existed no reasonable expectation of success in modifying the references to arrive at the claimed invention.

Applicants respectfully submit that one of ordinary skill in the art would have had no reasonable expectation of success in modifying the teachings of Reid with Faris and Brasile as suggested by the Examiner. Simply put, the scientific community held this view because it assumed that the liver autolyzes within less than an hour, and that progenitor cells—being particularly sensitive to ischemic damage—would be the first cells to die. Dr. Theise confirms this prejudice and the Examiner's review of the literature to-date confirms this statement. Declaration at 10. Together, the evidence lends convincing weight to Applicants assertion that one skilled in the art would *not* have expected any success in isolating progenitor cells from tissue greater than about 2 hours postmortem.

In conclusion, Applicants submit respectfully that the rejection of claims 1, 3, 4, 6-9, 12-21 and 23-34 under 35 U.S.C. § 103 has been traversed, and Applicants request respectfully that the rejection of same claims be withdrawn.

Double patenting

Claims 1, 2-4, 8-9, 12-21 and 23-34 stand rejected for alleged non-statutory obviousness-type double patenting over claims 1-4 of USP No. 6,069,055 or claims 1-32 of USP No. 6,242,252 in view of Faris and Brasile. The Examiner's reasons for rejection are set forth on

pages 11-13 and essentially reiterate the reasons for rejection under 35 U.S.C. § 103.[2] Applicants respectfully traverse this rejection. At least for the reasons expounded above in rebutting the Examiner's *prima facie* case for obviousness with the equivalent references, Applicants respectfully submit that the pending claims are not obvious over the cited patents.

Applicants believe that the present application remains in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

[2] The Reid reference, discussed hereinabove, is identical in disclosure to USP Nos. 6,069,005 and 6,242,252.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date January 8, 2008

By 

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Lola M. REID *et al.*
Title:	LIVER TISSUE SOURCE
Appl. No.:	09/764,359
Filing Date:	01/19/2001
Examiner:	Quang Nguyen
Art Unit:	1633
Confirmation Number:	7133

DECLARATION UNDER 37 C.F.R. § 1.132 OF NEIL THEISE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Neil Theise, declare as follows:

1. I have been asked by the Applicants of the subjection patent application to make this declaration to be submitted with its Response to the Final Office Action dated April 23, 2007. I am receiving remuneration for my time in preparing this Declaration; however, I have no other interest in the subject patent application or in the outcome of its prosecution.

2. I am currently a Professor of Pathology and a Professor of Medicine of Albert Einstein College of Medicine (AECOM), Yeshiva University, New York NY. I am attending physician in the Department of Pathology and the Department of Medicine (Division of Digestive Diseases) at Beth Israel Medical Center, affiliate hospital of AECOM, New York NY.

3. I received a Bachelors of Arts (Oriental Studies) and Bachelor of Applied Sciences (Computer Science) from the University of Pennsylvania in 1981. I graduated from Columbia University, College of Physicians and Surgeons with a Doctor of Medicine degree in 1986. Subsequent clinical training in Anatomic Pathology, generally, and subspecialty training in Liver Pathology and Liver Transplant Pathology followed, at Presbyterian Medical Center in New York, the Royal Free Hospital in London, England, and Mount Sinai Medical Center in New York. Attending positions followed at Mount Sinai Medical Center (1990-1994), Tisch Hospital of the New York University Medical Center (1994-2003), and Beth Israel Medical Center (2003 – present).

4. In addition to my clinical duties which involved full time service with the Mount Sinai and NYU liver transplant programs throughout my tenure at both institutions, including evaluation of donor grafts for transplantation and examination of many rejected donor livers, I have studied reperfusion injury to livers stored for transplantation surgery in animals and in humans and have personally researched human liver stem/progenitor cells throughout that time. Hence, I am intimately familiar with liver biology, including liver stem cell biology, and their viability for not only transplantation, but also in vitro modeling.

5. My liver stem cell research has focused on the location of the intrahepatic stem cell niche, beginning with publication in December of 1999 of the first confirmation in human livers that the canal of Hering is comprised of, or at least harbors, hepatic stem cells. Further studies in animals and in humans have confirmed the contribution of marrow-derived stem cells to hepatobiliary reconstitution in animals and in humans, both by direct differentiation and fusion with pre-existing hepatobiliary cells. I am considered an expert and pioneer in the identification of multiorgan stem cell plasticity. I have been the recipient of the following grants for studying these topics:

A. Innovative Seed Grant in Clinical Research in Primary Biliary Cirrhosis
American Liver Foundation
"Isolation and in vitro growth of bipotent progenitor cells from adult human livers."
July 1, 1998 to June 30, 2000
Principal Investigator

B. R01 DK58559-01A1
National Institutes of Health
"Hepatic engraftment of marrow cells in mice and humans."
October 1, 2001 to September 30, 2005
Principal Investigator

C. Singer-Hellman Research Grant
Beth Israel Medical Center of New York
"Medical induction of stem cell rescue from hepatic fulminant failure."
October 1, 2003 to September 30, 2004
Principal Investigator

D. Singer-Hellman Research Grant
Beth Israel Medical Center of New York
"Contributions of circulating progenitor cells to tumor growth."
October 1, 2004 to September 30, 2005
Principal Investigator

E. Pilot and Feasibility Study:
"Development of a murine model for detection of epithelial label retaining cells."
Marrion Bessin Liver Research Center, Albert Einstein College of Medicine
July 1, 2006 – June 30, 2007.
Principal Investigator

6. My educational background, work experience, and co-authored publications are described in my *curriculum vitae* attached as Exhibit A.

7. I have read and understood the Office Action dated March April 23, 2007 regarding the subject application. I also understand that the application is being rejected as obvious over PCT Application No. WO 95/13697 to Reid *et al* . ("Reid") in view of U.S. Patent No. 6,129,911 to Faris ("Faris") and U.S. Patent No. 5,843,024 to Brasile ("Brasile"). I disagree.

8. For the following reasons, I believe that that cited references fail to render the presently claimed invention obvious.

9. Foremost, I agree with the statement that "while methods of isolating liver precursor cells [were] known in the art, until the reduction to the practice of the present invention it was not known that progenitor cells can be isolated from what was considered in

the prior art as a 'useless' organ (citations omitted)." Specification, para. 0010. I also would agree that one having ordinary skill in the art would have deemed livers greater than 2 hours postmortem "useless" for isolating stem cells. In my experience of discussions at that time, while some in the field had considered the possibility of survival of stem/progenitor cells in post-mortem livers, no one had convincingly demonstrated that survival to generate a consensus, the majority responding with doubt, if not derision.

10. The reason why the scientific community believed livers greater than 2 hours postmortem were unsuitable for isolation of stem cells is because scientists adopted the then-current view that livers autolyze within less than an hour, and that progenitor cells were probably particularly sensitive to ischemic damage and would therefore be among the first cells to die.

11. The references cited by the Examiner confirm this widely held view at the time the subject application was filed. Reid and Faris both teach that procuring progenitor cells from liver tissue must take place "immediately" upon death. Brasile, also confirms the belief that a majority of livers become "non-functional" after just 30 minutes.

12. The Examiner believes that Faris teaches that liver tissues can be obtained from deceased donors and even cadavers "many hours or days after death." However, while Faris teaches the isolation of cells from cadavers immediately upon death, Faris no where explicitly (or implicitly) suggests the isolation of hepatic stem cells from cadavers "many hours or days after death." Rather, given Faris' working examples and state of the art at the time as I discuss above, one of ordinary skill in the art simply would not have interpreted Faris' comments to mean cadavers that are "about 2 hours to 30 hours postmortem."

13. Hence, it is my professional opinion that the present inventors' isolation of hepatic stem cells from cadavers that were "about 2 hours to 30 hours postmortem" to have

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[1] Applicants have previously argued that "useless" livers were defined in the context of livers "useless" for transplantation and provided evidence from the Scientific Registry of Transplant Recipients to support the conclusion that livers greater than about 2 hours postmortem would have been "useless."

been counter-intuitive at the time of the invention and was therefore unexpected to one of ordinary skill in the art at that time.

* * * * *

I hereby declare that all the statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements are so made punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: December 24, 2007

By: _____

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